REMARKS

Status of the Claims

Claims 1-2, 4-5, 7-15, 18-34, 37-39, 51-53, and 55-61 are pending. Claims 1-2, 4-5, 7-15, 18-34, 37-39, 51-53, and 55-61 are rejected. Claims 1, 32 and 49 are amended. Claims 3, 6-7, 13-31, 33-48, 50, and 54-57 are canceled herein. No new matter is added in any claim amendment.

Claim amendments

Claims 1 and 49 are amended to recite administering bismuth subnitrate or bismuth subcitrate in combination with a chelator(s) and a diuretic(s) and to incorporate therein the limitations of francium-221 and bismuth-213 daughters recited in claim 7. Also, claims 1 and 49 are amended to recite a "chelated" actinium-225 radioimmunoconjugate to clarify that actinium-225 radioimmunoconjugate comprises a chelant as recited in dependent claim 8. Claim 32 is amended to depend from amended independent claim 1 and to incorporate the limitation of cancer as the pathophysiological condition recited in claim 10 such that amended claim 32 now recites that scavenging bismuth-213 and inhibiting renal uptake of francium-211 increases the therapeutic index of the actinium-225 thereby improving the cancer treatment. No new matter is added in these amendments.

The 35 U.S.C. §103 Rejection

Claims 1-2, 7-11, 49, 51, and 57-60 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Kennel** *et al* (Cancer Biotherapy & Radiopharmaceuticals, 15:235-244, 2000) in view of **Satoh** *et al* (Eur. J. Cancer Clin Oncol., 25:1727-2731, 1989). Applicant respectfully traverses this rejection.

In considering independent claims 1 and 49, the Examiner states that **Kennel** *et al.* teach a method of treating lung cancer with alpha particles by administering Ac-225 bound to a HEHA-MAb 210B (Abstract). The Examiner also states that **Kennel** *et al.* teach that while the isotope coupled to the targeting monoclonal antibody delivers a tumoricidal dose to the lung, effectiveness of the therapy is limited by the associated radiotoxicity (pg.

242, 2nd col., last PP). The Examiner states that **Satoh** *et al.* teach the effects of preinduction of metallotheionein by bismuth subnitrate on the adverse effects and antitumor activity gamma ray irradiation in mice (Abstract) such as reducing bone marrow damage without compromising the tumor reducing effects (pg. 1730, 1st col., last PP). The Examiner concludes that it would be *prima facie* obvious to one of ordinary skill in the art to modify the method of **Kennel** *et al.* to include bismuth subnitrate in view of **Satoh** *et al.* who teach that bismuthsubnitrate pretreatment is an effective method for protection against side-effects in radiotherapy.

Kennel *et al.* disclose an evaluation of Ac-225 for vascular targeted radioimmunotherapy and teach that the potential for Ac-225 as radioimmunotherapeutic agent is compromised most importantly by the radiotoxicity associated with the decay daughter radioisotopes released from the target organ (Abstract). **Kennel** *et al* further teach lack of a conventional chelate that could withstand the energy released by radioactive decay of Ac-225 (page 243, 1st col., lines 2-4).

Satoh *et al.* disclose that the preinduction of metallothionein by bismuth subnitrate may prevent the adverse effects of gamma ray irradiation in mice (Abstract). A dose of 200 mg/kg prior to irradiation with a lethal dose of 6 Hy/leg of cobalt-60 suppressed leukocyte reduction and lipid peroxidation in bone marrow cells and increased metallothionein 2-fold therein (pg. 1728, 2nd col.). It is assumed that bismuth subnitrate induces an increased level of metallothionein which scavenges the free radicals induce by the gamma irradiation and thereby protects the bone marrow from gamma radiation injury (pg. 1729, 2nd col. to page 1730, 1st col., ll. 2).

Applicants have canceled claims 7 and 57. As recited in amended independent claims 1 and 49, Applicants invention is drawn to methods of reducing nephrotoxicity in an individual during radioimmunotherapeutic treatment of a pathophysiological condition and of increasing the therapeutic index of a DOTA-chelated actinium-225 radioimmunoconjugate. In both methods a combination of bismuth subnitrate or bismuth subcitrate and one or more chelators and one or more diruetics are administered to prevent renal accumulation or uptake of francium-221 and bismuth-213 daughters. This

action both reduces nephrotoxicity due to the daughters and increases the therapeutic index of actinium-225 upon reduction thereof.

A determination of obviousness requires a teaching or suggestion of all the claim elements in the combination of cited prior art which provides motivation for one of ordinary skill in the art to make the combination with a reasonable expectation of success not found in Applicants' specification. Also, the teachings of the prior art must be considered as a whole. First, **Kennel** *et al.* specifically state that although HEHA-chelated actinium-225 coupled to a targeting antibody may deliver a tumoricidal dose to the lung, the radiologic side effects due to release of daughter alphas limits the effectiveness of therapy. **Kennel** *et al.* also state that they know of no conventional chelant that would withstand the energy release (pg. 242, 2nd col., last PP).

No guidance is found in the combination as to what actinium-225 chelant would be effective to overcome the limitations to actinium-225 radiotherapy disclosed in **Kennel** *et al.* In fact **Kennel** *et al.* teach away from using a chelant, e.g., HEHA, and suggest, as an untested hypothesis, incorporating the actinium-225 into a stable molecule such as a fullerene which might be sufficient to retain the daughter isotopes. **Satoh** *et al.* teach using gamma radiation which teaches away from any alpha particle therapy. Thus, one of ordinary skill in the art would not be motivated to combine **Kennel** *et al.* with **Satoh** *et al.* since **Satoh** *et al.* neither teach or suggest a solution to the chelant problem disclosed in **Kennel** *et al.*

Second, the combination of **Kennel** *et al.* and **Satoh** *et al.* do not teach or suggest administering bismuth nitrate or bismuth citrate, one or more chelants and one or more diuretics to prevent renal accumulation or renal uptake of both francine-221 and bismuth-213 daughters. **Kennel** *et al.*, as discussed *supra*, hypothesize retaining the daughters within a fullerene or using a rapidly extravasating radioimmunoconjugate to trap the daughters within the tumor tissue to reduce accumulation (pg. 242, 2nd col., 1st PP). The disclosure of bismuth subnitrate in **Satoh** *et al.* does not remedy this deficiency.

At a minimum, **Satoh** *et al.* simply neither teach nor suggest administering a chelant and a diuretic with bismuth subnitrate. Also, as is known in the art, **Satoh** *et al.* teach that 6-9 Gys of gamma irradiation damage the bone marrow and other hematopoietic

tissues. The combination of **Kennel** *et al.* with **Satoh** *et al.* neither teach nor suggest that an accumulation via renal uptake of francium-221 and bismuth-213 daughters causes nephrotoxicity during an actinium-225 radioimmunotherapeutic treatment.

Nor do **Satoh** *et al.* teach or suggest that bismuth subnitrate will reduce renal accumulation or renal uptake of bismuth-221. **Satoh** *et al.* demonstrate that oral administration of bismuth subnitrate prior to gamma irradation reduces bone marrow ablation because bismuth subnitrate increases metallothionein in the bone marrow which scavenges free radicals therein caused by the gamma irradiation. Metallothionein also scavenges transition metals like cadmium, zinc, copper and mercury. Thus, bismuth can induce, but is not scavenged by metallothionein.

Applicants invention is drawn to a method of reducing nephrotoxicity by reducing renal accumulation of both francium-221 and bismuth-213, not to methods of reducing gamma ray radiotoxicity *per se*. Given the teachings in **Kennel** *et al.* in combination of **Satoh** *et al.* one of ordinary skill in the art would find no motivation to administer bismuth subnitrate, even by itself, to competitively block bismuth adsorption in the kidney. No teaching or suggestion is present in **Satoh** *et al.* that bismuth subnitrate interacts with or competitively blocks radiobismuth and/or the kidney in any manner. Certainly, given the absence in the combination of a teaching or suggestion to administer all of bismuth subnitrate or bismuth subcitrate with chelator(s) and diuretic(s) with a chelated actinium-225 immunoconjugate and a teaching or suggestion that renal accumulation of both francium-221 and bismuth-213 is reduced thereby, neither motivation nor a reasonable expectation of success are present for one of ordinary skill in the art.

Thus, absent a teaching or suggestion of these claim elements in the combination of **Kennel** *et al.* with **Satoh** *et al.*, no motivation is present for one of ordinary skill in the art to make the combination. Therefore, the combination of **Kennel** *et al.* with **Satoh** *et al.* cannot render amended independent claims 1 and 49 obvious. Furthermore, claims 2, 8-11 and 51 and 58-60 depend directly or indirectly from amended independent claims 1 and 49. If the combination of **Kennel** *et al.* with **Satoh** *et al.* cannot render amended independent claims 1 and 49 obvious, then neither are dependent claims 2, 8-11, 51, and 58-60 rendered obvious by the combination. Accordingly, in view of the claim

amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 1-2, 8-11, 49, 51, and 58-60 under 35 U.S.C. §103(a) be withdrawn.

Claims 4, 52 and 55 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Kennel** *et al.* in view of **Satoh** *et al*, as applied to claims 1-2, 7-11, 49, 51 and 57-60 above, in further view of **Jones** *et al.* (Nuclear Medicine & Biolgoy, 1996, 23:105-113, of record). Appliants respectfully traverse this rejection.

The Examiner states that **Kennel** *et al.* in view of **Satoh** *et al.* teach the claim elements of claims 1 and 49, as discussed *supra*, except for administering an adjuvant, such as a dithiol chelate, in combination with the actinium-225 conjugate and bismuth subnitrate. The Examiner also states that **Jones** *et al.* evaluate dithiol chelating agents DMPS and DMSA as adjuvants administered prior to and after the radioconjugate to accelerate clearance of bismuth and to reduce early and late accumulation of bismuth in the kidney (pg. 112, 2nd col., conclusion). The Examiner concludes it would be *prima facie* obvious for one of ordinary skill in the art to modify the method of **Kennel** *et al.* and **Satoh** *et al.* by including DMPS or DMSA as an adjuvant to accelerate bismuth clearance.

Jones *et al.* discloses that DMPS, which is more effective than DMSA, can be used as a potential adjuvant chelation therapy in lead-212 or bismuth-212 radioimmunotherapy protocols (Abstract).

Applicants have canceled claim 55. Claims 4 and 52 are dependent upon amended independent claims 1 and 49 and limit the chelator to specific dithiol chelating agents. For the reasons discussed *supra*, the combination of **Kennel** *et al.* with **Satoh** *et al.* cannot render claims 1 and 49 obvious. Including **Jones** *et al.* with this combination does not remedy all the deficiencies found in the combination of **Kennel** *et al.* and **Satoh** *et al.*

For the reasons presented *supra*, Applicants maintain that no motivation is present for one of ordinary skill in the art, upon viewing the combination of **Kennel** *et al.* and **Satoh** *et al.*, to use bismuth subnitrate to prevent renal accumulation of francium-221 and bismuth-213 during treatment of lung cancer with a Ac225-HEHA-MAb201B conjugate nor other chelated actinium-225 radioimmunoconjugate. Including **Jones** *et al.* does not remedy this deficiency because the reference only discloses using the dithiol chelating

agents DMPS or DMSA to chelate lead-213 or bismuth-212 during radiotherapy of various cancers. Nor does including **Jones** *et al.* with **Kennel** *et al.* and **Satoh** *et al.* remedy the lack of teaching or suggestion to use one or more diuretics with the bismuth subnitrate. At best, *arguendo*, one of ordinary skill in the art may be motivated to use DMPS or DMSA as adjuvants to chelate bismuth-213 daughters, but this is not Applicants' invention, as recited in amended independent claims 1 and 49 which recites administering all of bismuth subnitrate or bismuth subcitrate, chelator(s) and diuretic(s) to reduce nephrotoxicity.

Therefore, the combination of **Kennel** *et al.* with **Satoh** *et al.* and **Jones** *et al.* cannot render amended independent claims 1 and 49 obvious. As claims 4 and 52 are dependent upon claims 1 and 49, neither are these dependent claims rendered obvious by the combination. Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 4 and 52 under 35 U.S.C. §103(a) be withdrawn.

Claims 5, 53 and 56 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Kennel** *et al.* in view of **Satoh** *et al*, as applied to claims 1-2, 7-11, 49, 51 and 57-60 above, in further view of **Jones** *et al.* and **Schilcher** *et al.* (J. Can. Res. Clin. Oncol., 1984, 107:57-60). Applicants respectfully traverse this rejection.

The Examiner states that **Kennel** *et al.* in view of **Satoh** *et al.* teach the claim elements of claims 1 and 49, as discussed *supra*, except for administering a diruetic, such as furosemide, in combination with the actinium-225 conjugate and bismuth subnitrate. The Examiner also states that **Schilcher** *et al.* teach using the diruetic furosemide to prevent cumulative nephrotoxicity during an evaluation of fractionated low and high dose cisplatin for various tumors. The Examiner further states that **Jones** *et al.* teach that the kidney has been identified as a potential target for dose limitation toxicity from bismuth radiometal deposition (pg. 109, 2nd col, 1st PP; pg. 112, 1st col, 1st full PP). The Examiner concludes it would be *prima facie* obvious for one of ordinary skill in the art to modify the method of **Kennel** *et al.* and **Satoh** *et al.* by including furosemide because **Schilcher** *et al.* teach preventing cisplatin-induced cumulative nephrotoxicity and **Jones** *et al.* teach that the kidney is a potential target for toxicity from radiometal deposition.

Schilcher *et al* examine the effect of fractionated low and single high dose cisplatin in various tumors. **Schilcher** *et al* state that cisplatin therapy was associated with nephrotoxicity (page 59, col. 2, last PP) and that cumulative nephrotoxicity was prevented by prehydration and/or treatment with furosemide or mannitol (Summary, last sentence), although **Schilcher** *et al* do not support this assertion with any actual data. In fact, nephrotoxicity associated with the cisplatin therapy was observed in three patients (pg. 59, col. 1, 2nd full PP).

Applicants have canceled claim 56. Claims 5 and 53 are dependent upon amended independent claims 1 and 49 and limit the diuretic. For the reasons discussed *supra*, the combination of **Kennel** *et al.* with **Satoh** *et al.* and **Jones** *et al.* cannot render claims 1 and 49 obvious because, at a minimum, no motivation is present for one of ordinary skill in the art to use bismuth subnitrate to prevent renal accumulation of francium-221 and bismuth-213 during treatment of lung cancer with a Ac225-HEHA-MAb201B conjugate nor other chelated actinium-225 radioimmunoconjugate. Including **Schilcher** *et al.* with this combination does not remedy this deficiency. **Schilcher** *et al.* only state that cumulative nephrotoxicity from cisplatin chemotherapy was prevented by treatment with the diuretic furosemide, but do not provide any protocols for its use. Also, no teaching or suggestion is present in the combination that furosemide would be effective against francium-221 and bismuth-213 alpha particle-induced nephrotoxicity because cisplatin is a non-radiometal chemotherapeutic drug.

Therefore, the combination of **Kennel** *et al.* with **Satoh** *et al.*, **Jones** *et al.* and Schlicher *et al.* cannot render amended independent claims 1 and 49 obvious. As claims 5 and 53 are dependent upon claims 1 and 49, neither are these dependent claims rendered obvious by the combination. Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 5 and 53 under 35 U.S.C. §103(a) be withdrawn.

Claims 12 and 61 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Kennel** *et al.* in view of **Satoh** *et al.*, as applied to claims 1-2, 7-11, 49, 51, and 57-60, in further view of **McDevitt** *et al.* (Science 2001, 204:1537-1540, of record). Applicants respectfully traverse this rejection.

The Examiner states that **Kennel** *et al.* in view of **Satoh** *et al.* teach the claim elements of claims 1 and 49, as discussed *supra*, except for treating leukemia. The Examiner also states that **McDevitt** *et al.* teach a method of treating cancerous cells, e.g., prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancers, with an actinium-225-chelated conjugate (pg. 1537, Abstract). The Examiner concludes it would be *prima facie* obvious for one of ordinary skill in the art to modify the method of **Kennel** *et al.* and **Satoh** *et al.* to treat leukemia because **McDevitt** *et al.* teach that actinium-225 conjugates are effective to do so.

Kennel *et al.* and **Satoh** *et al.* are as described *supra* by the Examiner and by the Applicants. **McDevitt** *et al* examined tumor therapy with targeted atomic nanogenerators (Abstract). **McDevitt** *et al* examined the stability of Ac-225-DOTA-antibody constructs as potent tumor-selective molecular-sized generator in both established solid carcinomas or disseminated cancers (pg. 1538, 1st col, 2nd full PP). **McDevitt** *et al* also teach that the daughters of Ac-225 might be transferred to other sites such as the kidneys and intestine (pg. 1538, col.2, line 14-col.3, line 6).

Applicants' invention as recited in amended independent claims 1 and 49 is as described *supra*. Claims 12 and 61 are dependent upon amended independent claims 1 and 49 and limit the cancer to leukemia. For the reasons discussed *supra*, the combination of **Kennel** *et al.* with **Satoh** *et al.* cannot render claims 1 and 49 obvious because, at a minimum, no motivation is present for one of ordinary skill in the art to use bismuth subnitrate to prevent renal accumulation of francium-221 and bismuth-213 during treatment of lung cancer with a Ac225-HEHA-MAb201B conjugate nor other chelated actinium-225 radioimmunoconjugate.

Including **McDevitt** *et al.* with this combination does not remedy this deficiency. **McDevitt** *et al.* only disclose that actinium-225-DOTA linked to an appropriate internalizable antibody may be effective to treat leukemia and that francium-221 and bismuth-213 daughters can accumulate in the kidneys, but that pro*per se*lection of the internalizable antibody can help to retain the daughters within the cell (pg. 1540, 1st col., 1st full PP, last sentence). Therefore, **McDevitt** *et al.* does not remedy the deficiency in **Kennel** *et al.* with **Satoh** *et al.* of a teaching or a suggestion to administer the combination of

bismuth subnitrate or bismuth subcitrate and chelant(s) and diuretic(s) to prevent renal uptake of francium-221 and bismuth-213. In fact, the suggestion in **McDevitt** *et al.* would be for one of ordinary skill in the art to optimize the internalizable antibody in the actinium-225 conjugate in **Kennel** *et al.* to improve daughter retention and thereby reduce nephrotoxicity during treatment of leukemia or any cancer.

Therefore, the combination of **Kennel** *et al.* with **Satoh** *et al.* and **McDevitt** *et al.* cannot render amended independent claims 1 and 49 obvious. As claims 12 and 61 are dependent upon claims 1 and 49, neither are these dependent claims rendered obvious by the combination. Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 12 and 61 under 35 U.S.C. §103(a) be withdrawn.

Claims 1-2, 7-11, 49, 51, and 57-60 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Scheinberg** *et al* (U.S. Patent Pub. No. 2002/0058007) in view of **Satoh** *et al.* Applicant respectfully traverses this rejection.

In considering independent claims 1 and 49, the Examiner states that **Scheinberg** *et al.* teach a method of treating cancerous cells by administering an actinium-225 conjugate comprising a functionalized chelate (PP 0016). The Examiner also states that **Scheinberg** *et al.* disclose that histological analysis showed gastrointestinal mucosal sloughing and bone marrow hyplasia consistent with severe radiotoxicity (PP 0097). The Examiner states that **Satoh** *et al.* teach the effects of preinduction of metallotheionein by bismuth subnitrate on the adverse effects and antitumor activity gamma ray irradiation in mice (Abstract) such as reducing bone marrow damage without compromising the tumor reducing effects (pg. 1730, 1st col., last PP). The Examiner concludes that it would be *prima facie* obvious to one of ordinary skill in the art to modify the method of **Scheinberg** *et al.* to include bismuth subnitrate in view of **Satoh** *et al.* who teach that bismuth subnitrate pretreatment is an effective method for protection against side effects in radiotherapy.

Scheinberg *et al.* teach actinium-225 complexes comprising actinium-225 chelated to modified chelants and linked to a targeting agent which are delivered to cancerous cells such that the emitted alpha particles from actinium-225 and its daughters

effects treatment (Abstract). The actinium-225 complexes may treat solid and disseminated cancers such as prostate cancer, lymphoma, leukemia, neuroblastomas, breast cancer and ovarian cancer (PP 0037). Doses of actinium-225 above the mean tolerated dose cause gastrointestinal mucosal sloughing and bone marrow hyplasia consistent with severe radiotoxicity (PP 0097). Francium-221 and bisumuth-213 daughters from non-targeted actinium-225 complexes accumulate in the kidneys (0108). **Satoh** *et al.* is as described by the Examiner and by the Applicants.

Applicants have canceled claims 7 and 57. Applicants' amended independent claims 1 and 49 are as described *supra*. The scope of these claims encompasses reducing nephrotoxicity due to renal uptake of francium-221 and bismuth-213 during treatment with actinium-225 radioimmunoconjugates by administering all of bismuth subnitrate or bismuth subcitrate and chelant(s) and diruetic(s). Prevention of renal accumulation of the daughters improves the therapeutic index of the actinium-225.

First, the combination of **Scheinberg** *et al.* with **Satoh** *et al.* neither teach nor suggest bismuth subnitrate in combination with chelant(s) and diruetic(s) to prevent renal uptake of francium-221 and bismuth-213. Second, the combination of **Scheinberg** *et al.* with **Satoh** *et al.* neither teaches or suggests that bismuth subnitrate will reduce renal accumulation or renal uptake of bismuth-221. **Satoh** *et al.* demonstrate that oral administration of bismuth subnitrate prior to gamma irradation reduces bone marrow ablation because bismuth subnitrate increases metallothionein in the bone marrow which scavenges free radicals therein caused by the gamma irradiation. Metallothionein also scavenges transition metals like cadmium, zinc, copper and mercury. Thus, bismuth can induce, but is not scavenged by metallothionein.

Third, **Scheinberg** *et al.* teach that radiotoxicity, e.g., gastrointestinal mucosal sloughing and bone marrow hyplasia, occurs at doses above the mean therapeutic dose, but demonstrates that doses of the actinium-225 complex significantly below the MTD are effective against cancers. As is known in the art, **Satoh** *et al.* teach that side effects from therapeutic gamma irradiation include bone marrow lesions and intestinal injury (pg. 1729, 1st col., last PP). One of ordinary skill in the art would not be motivated to administer bismuth subnitrate during treatment with the actinium-225 complex in **Scheinberg** *et al.*,

because **Scheinberg** *et al.* disclose that lower doses of the Ac-225 complexes do not cause gastrointestinal mucosal sloughing and bone marrow hyplasia and are effective antitumor agents (PP 0097-0100; PP 0115-0125).

Therefore, given the teachings in **Scheinberg** *et al.* in combination of **Satoh** *et al.* one of ordinary skill in the art would find no motivation to administer bismuth subnitrate, even by itself, to competitively block bismuth adsorption in the kidney. No teaching or suggestion is present in **Satoh** *et al.* that bismuth subnitrate interacts with or competitively blocks radiobismuth and/or the kidney in any manner. Certainly, given the absence in the combination of a teaching or suggestion to administer all of bismuth subnitrate or bismuth subcitrate with chelator(s) and diuretic(s) with a chelated actinium-225 immunoconjugate and a teaching or suggestion that renal accumulation of both francium-221 and bismuth-213 is reduced thereby, neither motivation nor a reasonable expectation of success are present for one of ordinary skill in the art.

Thus, absent a teaching or suggestion of these claim elements in the combination of **Scheinberg** *et al.* with **Satoh** *et al.*, no motivation is present for one of ordinary skill in the art to make the combination. Therefore, the combination of **Scheinberg** *et al.* with **Satoh** *et al.* cannot render amended independent claims 1 and 49 obvious. Furthermore, claims 2, 8-11 and 51 and 58-60 depend directly or indirectly from amended independent claims 1 and 49. If the combination of **Scheinberg** *et al.* with **Satoh** *et al.* cannot render amended independent claims 1 and 49 obvious, then neither are dependent claims 2, 8-11, 51, and 58-60 rendered obvious by the combination.

Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 1-2, 8-11, 49, 51, and 58-60 under 35 U.S.C. §103(a) be withdrawn.

Claims 4, 52 and 55 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Scheinberg** *et al.* in view of **Satoh** *et al*, as applied to claims 1-2, 7-11, 49, 51 and 57-60 above, in further view of **Jones** *et al.* Applicants respectfully traverse this rejection.

The Examiner states that **Scheinberg** *et al.* in view of **Satoh** *et al.* teach the claim elements of claims 1 and 49, as discussed *supra*, except for administering an adjuvant, such as a dithiol chelate, in combination with the actinium-225 conjugate and bismuth subnitrate. The Examiner also states that **Jones** *et al.* evaluate dithiol chelating agents DMPS and DMSA as adjuvants administered prior to and after the radioconjugate to accelerate clearance of bismuth and to reduce early and late accumulation of bismuth in the kidney (pg. 112, 2nd col., conclusion). The Examiner concludes it would be *prima facie* obvious for one of ordinary skill in the art to modify the method of **Scheinberg** *et al.* and **Satoh** *et al.* by including DMPS or DMSA as an adjuvant to accelerate bismuth clearance.

Scheinberg *et al.*, **Satoh** *et al.* and **Jones** *et al.* are as described *supra* by the Applicants. Applicants' invention as recited in amended independent claims 1 and 49 is as described *supra*. Applicants have canceled claim 55. Claims 4 and 52 are dependent upon amended independent claims 1 and 49 and limit the chelator to specific dithiol chelating agents. For the reasons well discussed *supra*, the combination of **Scheinberg** *et al.* with **Satoh** *et al.* cannot render claims 1 and 49 obvious. Including **Jones** *et al.* with this combination does not remedy all the deficiencies found in the combination of **Scheinberg** *et al.* and **Satoh** *et al.* **Jones** *et al.* only disclose using the dithiol chelating agents DMPS or DMSA to chelate lead-213 or bismuth-212 during radiotherapy of various cancers. Therefore, **Jones** *et al.* does not remedy the lack of a suggestion or teaching in **Scheinberg** *et al.* with **Satoh** *et al.* to also include bismuth subnitrate or bismuth subcitrate and a diruetic(s) with DMPS or DMSA to reduce renal accumulation of francium-221 and bismuth-213.

Therefore, the combination of **Scheinberg** *et al.* with **Satoh** *et al.* and **Jones** *et al.* cannot render amended independent claims 1 and 49 obvious. As claims 4 and 52 are dependent upon claims 1 and 49, neither are these dependent claims rendered obvious by the combination. Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 4 and 52 under 35 U.S.C. §103(a) be withdrawn.

Claims 13-15, 18-34, 37-49, 51-53, 55-56, and 58-61 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Scheinberg** *et al.* in view of **Schilcher** *et al.* and in further view of **Jones** *et al.* Applicants respectfully traverse this rejection.

In considering independent claims 13, 32, 42, and 49, the Examiner states that **Scheinberg** *et al.* teach a method of treating cancerous cells by administering an actinium-225 conjugate comprising a functionalized chelate (PP 0016). The Examiner also states that **Scheinberg** *et al.* disclose that histological analysis showed gastrointestinal mucosal sloughing and bone marrow hyplasia consistent with severe radiotoxicity (PP 0097). The Examiner further states that **Scheinberg** *et al.* disclose that bismuth-213 accumulates in the kidney as a result of decay from nontargeted constructs (PP 0108). The Examiner states that **Schilcher** *et al.* teach the use of the diuretic furosemide for the prevention of cumulative nephrotoxicity during fractionated low and single high dose cisplatin treatment of various cancers (Abstract). The Examiner also states that **Jones** *et al.* evaluate dithiol chelating agents DMPS and DMSA as adjuvants administered prior to and after the radioconjugate to accelerate clearance of bismuth and to reduce early and late accumulation of bismuth in the kidney (pg. 112, 2nd col., conclusion). The Examiner concludes it would be *prima facie* obvious for one of ordinary skill in the art to modify the method of **Scheinberg** *et al.* by including one or both of a diruetic or a dithiol chelator because **Schilcher** *et al.* teach preventing cisplatin-induced cumulative nephrotoxicity and **Jones** *et al.* teach that the kidney is a potential target for toxicity from radiometal deposition.

Scheinberg *et al.*, **Schilcher** *et al.* and **Jones** *et al.* are as stated by the Applicants *supra*. Applicants have canceled claims 13-15, 18-31, 33-34, 37-48, and 55-56. Claim 32 is amended to depend from amended independent claim 1 which is not cited in this rejection. Amended independent claim 49 is as discussed *supra*. The combination of **Scheinberg** *et al.*, **Schilcher** *et al.* and **Jones** *et al.* does not teach or suggest inhibiting renal uptake of both francium-221 and bismuth-213 daughters via administration of **all** of bismuth subnitrate or bismuth subcitrate and chelator(s) and diruetic(s). Particularly, the combination neither teaches nor suggests either bismuth subnitrate or bismuth subcitrate.

Therefore, the combination of **Scheinberg** *et al.* with **Schilcher** *et al.* and **Jones** *et al.* cannot render amended independent claim 49 obvious. As claims 51-53 and 58-

61 are dependent upon claim 49, neither are these dependent claims rendered obvious by the combination. Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 49, 51-53 and 58-61 under 35 U.S.C. §103(a) be withdrawn.

Claims 13-15, 18-34, 37-49, 51-53, 55-56, and 58-61 are rejected under 35 U.S.C. §103(a) as being unpatentable over **McDevitt** *et al.* in view of **Schilcher** *et al.* and in further view of **Jones** *et al.* Applicants respectfully traverse this rejection.

In considering independent claims 13, 32, 42, and 49, the Examiner states that **McDevitt** *et al.* teach a method of treating cancerous cells, e.g., prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancers, with an actinium-225-chelated conjugate (pg. 1537, Abstract).. The Examiner also states that **McDevitt** *et al.* disclose that bismuth-213 accumulates in the kidney as a result of decay from nontargeted constructs (pg. 1538; Fig. 1B). The Examiner states that **Schilcher** *et al.* teach the use of the diuretic furosemide for the prevention of cumulative nephrotoxicity during fractionated low and single high dose cisplatin treatment of various cancers (Abstract). The Examiner also states that **Jones** *et al.* evaluate dithiol chelating agents DMPS and DMSA as adjuvants administered prior to and after the radioconjugate to accelerate clearance of bismuth and to reduce early and late accumulation of bismuth in the kidney (pg. 112, 2nd col., conclusion). The Examiner concludes it would be *prima facie* obvious for one of ordinary skill in the art to modify the method of **McDevitt** *et al.* by including one or both of a diruetic or a dithiol chelator because **Schilcher** *et al.* teach preventing cisplatin-induced cumulative nephrotoxicity and **Jones** *et al.* teach that the kidney is a potential target for toxicity from radiometal deposition.

McDevitt *et al.*, **Schilcher** *et al.* and **Jones** *et al.* are as stated by the Applicants *supra*. Applicants have canceled claims 13-15, 18-31, 33-34, 37-48, and 55-56. Claim 32 is amended to depend from amended independent claim 1 which is not cited in this rejection. Amended independent claim 49 is as discussed *supra*. The combination of **McDevitt** *et al.*, **Schilcher** *et al.* and **Jones** *et al.* does not teach or suggest inhibiting renal uptake of both francium-221 and bismuth-213 daughters via administration of **all** of bismuth

subnitrate or bismuth subcitrate and chelator(s) and diruetic(s). Particularly, the combination neither teaches nor suggests either bismuth subnitrate or bismuth subcitrate.

Therefore, the combination of **McDevitt** *et al.* with **Schilcher** *et al.* and **Jones** *et al.* cannot render amended independent claim 49 obvious. As claims 51-53 and 58-61 are dependent upon claim 49, neither are these dependent claims rendered obvious by the combination. Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 49, 51-53 and 58-61 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed August 27, 2007. Applicants submit that claims 1-2, 4-6, 8-12, 32, 49, 51-53, and 58-61 are in condition for allowance and request that claims 1-2, 4-6, 8-12, 32, 49, 51-53, and 58-61 be passed to issuance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution. Applicants include a Petition for a One Month Extension of Time. Please charge the $60 petition fee to the credit card identified on the enclosed Form PTO-2038. Only in the absence of Form PTO-2038, please debit any applicable fees from Deposit Account No. 07-1185, upon which the undersigned is allowed to draw.

Respectfully submitted,

Date: Dec 26, 2007

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